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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,860	11/14/2001	Kuang Yu Chen	RU-0173	6007

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,860	CHEN ET AL.	
	Examiner	Art Unit	
	Michele C. Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-37* is/are pending in the application.

4a) Of the above claim(s) *1-3,10,11 and 16-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *6-9,12-15 and 30-37* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0203* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on September 25, 2003.

Claims 6-9, 12-15 and 30-37 are under examination. The claims have been examined, insofar, as they read on the elected invention, namely orange peel extract and cancer.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections35 USC § 112

Claims 6-9 and 12-15 as amended, and newly submitted Claims 30-37 remain and/or are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for an *in vitro* method of inhibiting the growth of cancer cells comprising administering an effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines and/or an *in vivo* method of inhibiting the growth of cancer cells in mice comprising administering to mice an effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate, does not reasonably provide enablement for a method of treating any and all diseases or conditions in any and all animals by modulating Cox-2-gene expression comprising administering to any and all animals the claim-designated composition. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a method for preventing or treating a disease or a condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising a theaflavin-3-gallate and theaflavin-3'-gallate, wherein said mixture is present in an amount sufficient to modulate the Cox-2 gene expression, and wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. The claims are further directed to a method wherein the disease or condition is cancer; wherein the cancer is colorectal cancer; and, wherein the composition further comprises an orange peel extract.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Firstly, Applicant argues that the presence of both anticipation and enablement rejection in the previous Office action against the same claims appears contradictory. In an attempt to support the argument, Applicant points to the teachings of the cited reference of Yang et al. stating, "If the Examiner believes Yang enables the method of

treating cancer using black tea extracts *In vivo*, then the enablement rejection must be withdrawn." However, Applicant's arguments are not persuasive because they are not directed to the limitations of the presently claimed invention. Moreover, while Applicant has demonstrated an *in vitro* method for the inhibition of the growth for two cancerous cell lines (*i.e.,* virally transformed W138VA cells and Caco-2 human colon cancer cells) comprising the administration of a black tea extract comprising theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines in an amount sufficient to inhibit cancer cell growth, Applicant has not demonstrated a method for treating any and all diseases or conditions in any and all animals by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression. Furthermore, Applicant has not disclosed a method for treating any and all disease conditions in any and all animals by modulating Cox-2 gene expression, wherein the composition further comprises an orange peel extract. For example, on page 6 of the application, lines 6-34, Applicant alleges that the effect of TF-2 on Cox-2 gene expression was examined in the aforementioned cancer cells. On page 11 of the specification, lines 15-33, bridging pages 12-14, Applicant discloses assays for DNA fragmentation analysis, Northern Blot analysis, Reverse transcription polymerase chain reaction, and Western Blot analysis, **however, nowhere in the specification does Applicant show the data from which Applicant has concluded that the claim designated extract has an effect on modulating Cox-2 gene expression**. While it may be possible that the composition, as recited in the claims,

could be useful for the claimed functional effect in treating mice, it seems highly unlikely that the claimed method of treatment could be used for the treatment of any and all diseases or conditions in any and all animals by modulating Cox-2 gene expression given the limited data and experimental models shown by Applicant, even after extensive experimentation.

Applicant also argues that the *in vitro* models used in the present application are acceptable models for animals including humans with naturally occurring tumors and the data obtained thereof is sufficient to convince one of skill in the art of the asserted utility of the present application. Applicant's argument is unpersuasive because the data obtained from the demonstrated *in vitro* models of cancer cell growth inhibition does not extrapolate or directly correlate to cancer growth inhibition in humans for the reasons set forth below. The Office notes that while the claims do not expressly direct using the claim-designated black tea extract or composition comprising the claim-designated theaflavin mixture for treating cancer cells in humans, the specification does teach delivering the claim-designated plant extract comprising the claim-designated theaflavin mixture to human cancer cell lines and the functional effect of cell growth inhibition and decrease in the level of Cox-2 protein. Moreover, the specification suggests that the mechanism by which the claim-designated plant extract exerts its anti-tumor effect is the modulation of Cox-2 gene expression. The Office further notes that on pages 7, 8, and 9, lines 1-29, Applicant discloses the development of nutraceutical dietary supplements comprising the black tea extract of the claimed invention for human consumption. The specification clearly provides a prophetic method for preventing or

treating a disease or condition in an animal by modulating Cox-2 gene expression comprising administering to an animal the claimed black tea extract in an amount sufficient to modulate Cox-2 gene expression, wherein the disease or condition is cancer, wherein the cancer is colorectal cancer, and wherein the composition further comprises an orange peel extract. It should be noted that the state of the art at the time of filing suggests that the delivery of therapeutic drugs which exhibit *in vitro* anti-tumor activity do not necessarily have the same beneficial functional effect in humans. For example, Jain (Science, 1996. Vol. 271: 1079-1080) discloses that while promising chemotherapeutic agents exhibit activity against cancer cells *in vitro* and *in vivo* tumor systems, these same agents heralded as breakthrough drugs do not have the same functional effect in humans when delivered to humans bearing tumors. In another example, Dermer (Bio/Technology, 1994. Vol. 12: 320) states, "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body."

Claims drawn to methods intended for the administration of compounds to cancer cells and/or cancer patients, or in the instant case, claims drawn to methods treating a disease or condition in an animal by modulating Cox-2 gene expression (which may induce the growth of cancerous cells), generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the therapeutic effective amounts of the composition comprising the active ingredients intended for the therapeutic treatment for

modulating Cox-2 gene expression a disease or a condition in any and all animals comprising administering to any and all animals the claim-designated composition in an amount sufficient to modulate Cox-2 gene expression. There is no guidance in the specification, other than the aforementioned examples directed to the delivery of an effective amount of black tea extract which comprises a mixture of theaflavin-3-gallate and theaflavin-3'-gallate to *in vitro* cancer cell cultures for the reduction of cell number and decrease in the level of Cox-2 protein. Applicant further argues that the specification does provide sufficient disclosure to enable those skilled in the art to practice the full scope of the claims without undue experimentation. However, as set forth in the previous Office action, given the insufficient guidance in the specification as to how to carry out the instantly claimed invention for the proposed method of therapeutic treatment, the lack of working examples, and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

According, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the claim-designated composition would have the claimed functional effect for treating any and all diseases or conditions in any and all animals by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression wherein the disease or condition is cancer, wherein the cancer is colorectal cancer, and

wherein the composition further comprises an orange peel, as broadly claimed, other than the demonstrated *in vitro* and/or *in vivo* method of treating cancer in mice.

Claim Rejections - 35 USC § 102

Claims 6-8 and 12-14, as amended, remain rejected under rejected under 35 U.S.C. 102(a) as being anticipated by Yang et al. (U). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant claims a method for treating a disease condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate mixture, wherein said mixture is present in an amount sufficient to modulate the Cox-2 gene expression wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 6, wherein the disease or condition is cancer. Applicant further claims the method of claim 7, wherein the cancer is colorectal cancer. Applicant further claims a method for treating a disease condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising theaflavin-3-gallate and theaflavin-3'-gallate mixture is present in an amount sufficient to modulate the Cox-2 gene expression, wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 12, wherein the disease or condition is cancer. Applicant further claims the method of claim 13, wherein the cancer is colorectal cancer.

Applicant argues that Yang fails to anticipate the instantly claimed invention because Yang teaches that the prior art preparations must contain all theaflavins (*i.e.,* theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate and theaflavin-3, 3'-digallate), EGCG, EGC, ECG and EC. However, Applicant's arguments are not persuasive because, on page 196, lines 7-10, Yang teaches an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate. On page 194, lines 6-19 bridging page 195, lines 1-12, Yang teaches that the administration of an extract of black tea (DBT) inhibits lung tumorigenesis in mice treated with 1-(methylnitrosamino)-1-(3-pyridyl)-butanone (NNK). In a NNK-induced lung tumorigenesis model, Yang further teaches that administering DBT inhibits adenoma formation and cell proliferation (see page 195, line 19 to page 197, lines 1-11). On page 199, lines 27-35, Yang teaches, "Tea inhibits the activity of several enzymes related to tumor promotion and cell proliferation, including ornithine decarboxylase, protein kinase C, cyclooxygenase, and lipoxygenase." Applicant also argues, "The Yang reference is also explicit in that the black tea preparation must contain all the theaflavins." However, Applicant's argument is not commensurate in scope to the limitations of the claimed invention as Applicant's claimed method is directed to a method for treating a disease condition in an animal by modulating Cox-2 gene expression comprising the administration of a sufficient amount of a black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate mixture and a method of treating a disease or a condition in an animal by modulating Cox-2 gene expression comprising the administration of a sufficient amount of a composition which comprises theaflavin-3-gallate and theaflavin-3'-gallate. As Yang

teaches a method of administering the claim-designated composition, the method taught by Yang is considered to anticipate the claimed subject matter.

Applicant further argues that Yang fails "to appreciate the fact that a sufficient amount of a mixture of theaflavin-3-gallate and theaflavin-3'-gallate (together known as TF2) to modulate Cox-2 expression and to treat a disease or condition in an animal." While Applicant may have elucidated the molecular mechanism wherein the claim-designated theaflavins contained therein the black extract taught by Yang provide the beneficial functional effect of treating the claim-designated disease conditions in an animal, wherein the molecular mechanism is modulation of Cox-2 gene expression, Applicant has not provided adequate evidence to the contrary that the composition of the prior art teaching does not comprise a sufficient amount of a mixture of theaflavin-3-gallate and theaflavin-3'-gallate, as instantly claimed. The Office notes that Yang does not expressly teach his method of treating cancer comprising the administration to animals an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate as a method to modulate Cox-2 gene expression. However, as the composition taught by Yang comprises the claimed ingredients obtained from an extract of black tea and the claimed method is a one step method for the administration of the same ingredients having the same and identical functional effect of treating the same disease conditions, the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by Yang because cancer is associated with Cox-2 gene expression. Please note that since the prior art procedure teaches the administration of the same ingredients to provide the functional effect of treating the

same disease condition as claimed, the prior art procedure inherently must prevent colorectal cancer because the same ingredient is applied in the same way. In re Best 195 USPQ 430, 433 (CCPA 1977). Thus, the prior art procedure reads on treating colorectal cancer. Finally, Applicant argues that the rejection based on inherent anticipation is improper and contradicts the restriction requirement of the Office action dated November 18, 2002, because the Office states "the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by Yang because cancer is associated with Cox-2 gene expression." However, Applicant's argument is not persuasive because as set forth in the previous Office action requiring a restriction requirement, it is true that cancer or tumor growth does not necessarily have to be associated with Cox-2 gene expression

The teachings of Yang are deemed to anticipate the claimed subject matter.

Claims 6-8 and 12-14, as amended, and newly submitted Claims 30-32, and 34-36 remain and/or are rejected under rejected under 35 U.S.C. 102(a) as being anticipated by DE 19627344 (O and U1, translation provided herein). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant's claimed invention of Claims 6-8 and 12-14 was set forth above. Applicant further claims a method for treating a disease condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising theaflavins consisting essentially of theaflavin-3-gallate and

theaflavin-3'-gallate mixture is present in an amount sufficient to modulate the Cox-2 gene expression, wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 30, wherein the disease or condition is cancer. Applicant further claims the method of claim 31, wherein the cancer is colorectal cancer. Applicant further claims a method for treating a disease or a condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition consisting essentially of theaflavin-3-gallate and theaflavin-3'-gallate mixture, wherein said mixture is present in an amount sufficient to modulate the Cox-2 gene expression wherein the disease is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 34 wherein the disease or condition is cancer. Applicant further claims the method of claim 35, wherein the cancer is colorectal cancer.

Applicant argues that DE 19627344 fails to anticipate the claimed subject matter because the prior art is explicit in that the referenced composition must contain all theaflavins. However, this is not persuasive because DE 19627344 teaches an extract of *Camellia sinensis* comprising theaflavin-3-gallate and theaflavin-3'-gallate which is used for the prevention or treatment of cancer. Contrary to Applicant's arguments, the prior art reference does not require that the composition must contain all theaflavins. For instance, DE 19627344 expressly teaches that the referenced composition contains one, several, or all of the following substances: (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin-3-gallate, (-)-epigallocatehcin-3-gallate, theaflavin (TF-1), theaflavin-monogallate A (TF-2A), theaflavin-monogallate B (TF-2B), and theaflavin-digallate B

(TF-3) for the treatment of disease conditions, such as cancer, rheumatism, and inflammatory diseases. Furthermore, while Applicant may have elucidated the molecular mechanism wherein the claim-designated theaflavins contained therein the black extract taught by DE 19627344 provide the beneficial functional effect of treating the claim-designated disease conditions in an animal, wherein the molecular mechanism is modulation of Cox-2 gene expression, Applicant has not provided adequate evidence to the contrary that the composition of the prior art teaching does not comprise a sufficient amount of a mixture of theaflavin-3-gallate and theaflavin-3'-gallate, as instantly claimed. The Office notes that DE 19627344 does not expressly teach his method of treating cancer comprising the administration to animals an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate as a method to modulate Cox-2 gene expression. However, as the composition taught by DE 19627344 comprises the claimed ingredients obtained from an extract of black tea and the claimed method is a one step method for the administration of the same ingredients having the same and identical functional effect of treating the same disease conditions, the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by DE 19627344 because cancer is associated with Cox-2 gene expression. Please note that since the prior art procedure teaches the administration of the same ingredients to provide the functional effect of treating the same disease condition as claimed, the prior art procedure inherently must prevent colorectal cancer because the same ingredient is applied in the same way. In

re Best 195 USPQ 430, 433 (CCPA 1977). Thus, the prior art procedure reads on a method of treating colorectal cancer.

It is noted that the claims now recite the administered composition as one "consisting essentially of a composition comprising theaflavins consisting essentially of theaflavin-3-gallate and theaflavin-3'-gallate mixture". It is also noted that the composition disclosed in the cited prior art contains numerous ingredients in addition to the claim-designated theaflavin mixture recited in Applicant's claims. MPEP § 2111.03 clearly states that "[t]he transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or step 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." (Citations omitted, emphasis in original). Moreover, MPEP § 2111.03 states that claims recited in "consisting essentially of" language should be construed as if recited in open "comprising" language, absent some evidence that the additional ingredients in the prior art process/product materially affect the basic novel properties of the claimed invention:

For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., *PPG [Industries v. Guardian Industries],* 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase 'consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the

invention.") See also *In re Janakirama-Rao*, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1936).

On the current record there is no evidence that any of the additional ingredients present in the prior art composition would affect the basic and novel properties of the prior art composition such that the prior art composition is truly different than the claimed composition. Thus, applicant's claims must be construed as if reciting "comprising" language, thereby encompassing the additional ingredients in the prior art composition, despite the "consisting essentially of" language. A holding of anticipation/obvious is therefore required.

Lastly, note specifically that MPEP § 2111.03 further provides that "[w]hen an applicant contends that additional steps or materials in the prior art are excluded by the recitation of 'consisting essentially of,' applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention." (Citations omitted.)

Finally, Applicant argues that the rejection based on inherent anticipation is improper and contradicts the restriction requirement of the Office action dated November 18, 2002, because the Office states "the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by DE 19627344 because cancer is associated with Cox-2 gene expression." However, Applicant's argument is not persuasive because as set forth in the previous Office action requiring a restriction requirement, it is true that cancer or tumor growth does not necessarily have to be associated with Cox-2 gene expression

Therefore, the cited reference is deemed to anticipate the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 6-9 and 12-15 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (U) in view of Okuda et al. (N) and Xu et al. (V).

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Yang were relied upon for the reasons set forth above. Yang taught the claimed invention except for orange peel extract. Therefore, the secondary references of Okuda and Xu were relied upon because Okuda and Xu teach methods of administering orange peel extract to animals in the treatment of diseases associated with Cox-2 gene expression, such as cancer. Firstly, Okuda teaches a composition comprising an extract of CHINPI (peel of *Citrus aurantium* or orange peel), which inhibited the fat decomposition accelerating action of cancer toxin (toxohormone L) and promoted the

lipid metabolism and appetite of a patient suffering cancer. Secondly, on page 331, column 2, lines 1-12, Xu teaches that supplementing the diets of human subjects with orange peel powder inhibited the formation of N-nitrosoproline (NPRO). See Figure 3, also. Note that Xu teaches that the NRPO test with L-proline was used as a probe to observe N-nitrosation potential in populations in high-risk areas for gastric cancer.

Thus, with Yang providing the motivation of administering to an animal a black tea extract which comprises a theaflavin-3-gallate and theaflavin-3'-gallate mixture to treat cancer, and with Yang teaching that orange peel extract has extremely low toxicity and high safety; and, finally with Xu suggesting that orange peel extract contains constituents that can block the carcinogenic process and in particular inhibit the endogenous formation of carcinogenic N-nitroso compounds (NOC), on page 332, column 2, lines 34-45, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the instantly claimed old and well-known ingredients to provide the instantly claimed method for the treatment of cancer, as suggested by the cited references. As each of the references clearly indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by that reference. Therefore, the invention as a whole was clearly *prima facie* obvious in the absence to the contrary.

Claims 6-8 and 12-14 as amended, and newly submitted Claims 30-32, and 34-36 remain and/or are rejected under rejected under rejected under 35 U.S.C. 103(a) as being unpatentable over DE 19627344 (O and U1, translation provided herein) in view of Okuda et al. (N) and Xu et al. (V).

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of DE 19627344 were relied upon for the reasons set forth above. DE 19627344 taught the claimed invention except for orange peel extract. Hence, the secondary references of Okuda and Xu were relied upon because Okuda and Xu teach methods of administering orange peel extract to animals in the treatment of diseases associated with Cox-2 gene expression, such as cancer. Firstly, Okuda teaches a composition comprising an extract of CHINPI (peel of *Citrus aurantium* or orange peel), which inhibited the fat decomposition accelerating action of cancer toxin (toxohormone L) and promoted the lipid metabolism and appetite of a patient suffering cancer. Secondly, on

page 331, column 2, lines 1-12, Xu teaches that supplementing the diets of human subjects with orange peel powder inhibited the formation of N-nitrosoproline (NPRO). See Figure 3, also. Note that Xu teaches that the NRPO test with L-proline was used as a probe to observe N-nitrosation potential in populations in high-risk areas for gastric cancer.

Thus, with DE 19627344 providing the motivation of administering to an animal a black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate mixture to provide to treat cancer, and with Yang teaching that orange peel extract has extremely low toxicity and high safety; and, finally with Xu suggesting that orange peel extract contains constituents that can block the carcinogenic process and in particular inhibit the endogenous formation of carcinogenic N-nitroso compounds (NOC), on page 332, column 2, lines 34-45, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the instantly claimed old and well-known ingredients to provide the instantly claimed method for the treatment of cancer, as suggested by the cited references. As each of the references clearly indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by that reference. Therefore, the invention as a whole was clearly *prima facie* obvious in the absence to the contrary.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

MCF

December 15, 2003

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600